

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 May 2001 (25.05.2001)

PCT

(10) International Publication Number
WO 01/36383 A1

(51) International Patent Classification: C07C 303/34,
C07D 263/26, C07C 307/10

(74) Agents: HAY, Martin, A. et al.; Eli Lilly and Company,
Lilly Corporate Center, Indianapolis, IN 46285 (US).

(21) International Application Number: PCT/US00/28877

(22) International Filing Date:
3 November 2000 (03.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9927302.1 18 November 1999 (18.11.1999) GB

(71) Applicant (for all designated States except US): ELI
LILLY AND COMPANY [US/US]; Lilly Corporate
Center, Indianapolis, IN 46285 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

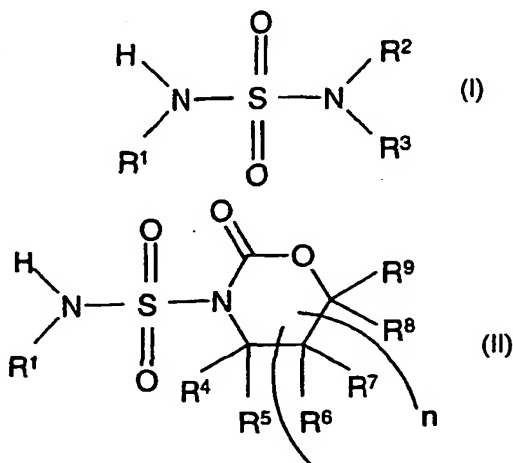
(75) Inventors/Applicants (for US only): ANTOINE, Luc,
Jean, Jules [BE/BE]; Sonvalwijk 49, B-3401 Landen
(BE). BORGHESE, Alfio [IT/BE]; Dreve M. Davout 21,
B-1470 Baisy-Thy (BE). VAN HOECK, Jean-Pierre,
Joseph, Sylvain [BE/BE]; Rue Gaston Delvaux 76,
B-1475 Chastre (BE).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF SULFAMIDES



(57) Abstract: A process for the production of an aryl sulfamide having formula (I), in which R¹, R² and R³ are each hydrogen, alkyl, cycloalkyl or aryl, provided that at least one of R¹, R² and R³ is aryl, which comprises reacting a compound of formula (II) where R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are each hydrogen, alkyl or aryl, and n is 0 or 1, with an amine of the formula R²R³NH (III), in the presence of a strong base.

WO 01/36383 A1

PROCESS FOR THE PREPARATION OF SULFAMIDES

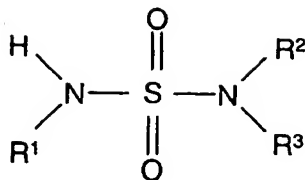
This invention relates to a process for producing
sulfamides, and to novel intermediates used in the
5 process.

Sulfamides are conventionally prepared by the use of
strongly electrophilic reagents such as sulfamoyl
chloride, sulfonyl dichloride, phosphorus oxychloride or
10 phosphorus pentachloride. Belgian patent 667.311
discloses a method of making sulfamides employing an
N-alkyl sulfamoyl chloride. However, all such reagents
involve aggressive synthetic methods, and indeed can be
inconvenient or dangerous in their practical,
15 industrial, application.

The invention provides a process for the production of
aryl sulfamides that avoids the use of the above
hazardous materials and conditions, and gives a high
20 yield.

The process of the invention is for the production of an
aryl sulfamide having the formula

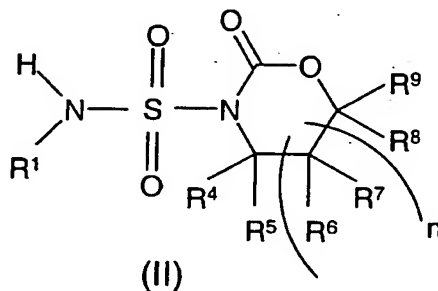
- 2 -



(I)

in which R¹, R² and R³ are each hydrogen, alkyl,
 cycloalkyl or aryl, provided that at least one of R¹, R²
 5 and R³ is aryl,

which comprises reacting a compound of the formula



(II)

10

where R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are each hydrogen, alkyl
 or aryl, and n is 0 or 1, with an amine of the formula
 R²R³NH (III), in the presence of a strong base.

15 The reaction can be carried out at ambient temperature
 or at the reflux temperature of the solvent in which the

reaction is performed, and generally the temperature of the reaction is chosen in the range of from 0° C. to 100° C. A polar, aprotic, solvent is preferred, as, for example, acetonitrile.

5

A strong base is required for the reaction to proceed, and examples include triethylamine,

1,8-diazabicyclo[5,4,0]undec-7-ene (DBU),

1,5-diazabicyclo[4,3,0]non-5-ene (DBN) or

10 1,4-diazabicyclo[2,2,2]octane (TED). Preferably from one to three equivalents of base are employed.

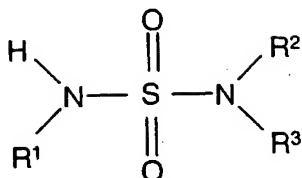
In the above formulae, an alkyl group can be substituted or unsubstituted, and is preferably C₁₋₆ alkyl, being
15 branched or unbranched. A cycloalkyl group preferably containing from 3 to 9 carbon atoms, and may, for example, be substituted by one to three alkyl groups such as methyl. When substituted, the alkyl group can be substituted by halo, C₁₋₆ alkoxy, C₃₋₉ cycloalkyl,
20 optionally substituted phenyl or optionally substituted heteroaryl. An aryl group can be, for example, naphthyl or, preferably, phenyl, and can be substituted or unsubstituted. A substituted aryl group is substituted with one or more, preferably one to three, substituents

selected from, for example, an electron-donating
substituent such as, for example, C₁₋₄ alkyl, C₁₋₄
alkoxy, C₁₋₄ alkylthio, hydroxy, amino, or an electron-
withdrawing substituent such as, for example, carboxy,
5 nitro, cyano, trifluoromethyl, halo, C₁₋₄ alkyl-SO- and
C₁₋₄ alkyl-SO₂-.

Preferably, R¹, R² and R³ are selected from hydrogen,
C₁₋₆ alkyl and optionally substituted phenyl. In
10 formula (II) above, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are
preferably hydrogen, and n is preferably 0. It may,
nevertheless, be desirable to employ a terminal moiety
in which one or more of R⁴ to R⁹ is alkyl or aryl, for
instance, in the preparation of stereoisomers.

15

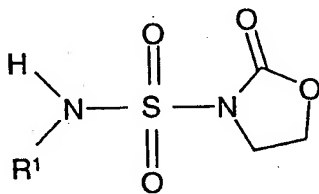
It has been found that the nature of the substituent on
an aryl group, for example a substituted phenyl, can
surprisingly affect the reaction. Electron-donating
substituents assist the reaction. Thus it is preferred
20 that the substituent R¹ is optionally substituted alkyl
or phenyl optionally substituted with an electron-
donating substituent, and a preferred process is one for
the preparation of a compound of the formula



in which R¹ is alkyl or phenyl optionally substituted
5 with an electron-donating substituent, and R² and R³ are
each hydrogen, alkyl or optionally substituted phenyl,
provided that R¹ is phenyl optionally substituted with
an electron-donating substituent and/or R² is optionally
substituted phenyl,

10

which comprises reacting a compound of the formula



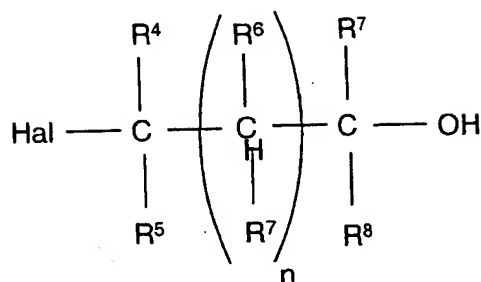
(IV)

15 with an amine of the formula R²R³NH, in the presence of
a strong base. A particularly preferred process is one
for the production of a compound of the above formula in

which R¹ is C₁₋₆ alkyl or phenyl optionally substituted with an electron-donating substituent, R² is C₁₋₆ alkyl or optionally substituted phenyl, and R³ is hydrogen, provided that R¹ is phenyl optionally substituted with
5 an electron-donating substituent and/or R² is optionally substituted phenyl.

Compounds of formula (IV) where R¹ is phenyl optionally substituted with an electron-donating substituent are
10 novel, with the exception of compounds in which R¹ is 3-methylbutyl or phenyl, and these novel compounds are included as an aspect of the present invention. They are stable, mainly crystalline solids, which can be readily isolated from the reaction medium.

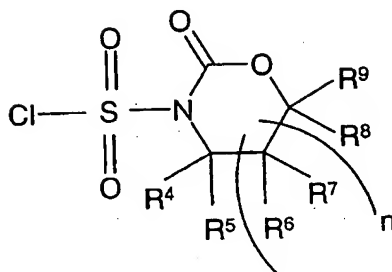
15
Compounds of formula R²R³NH (III) employed in the above reactions are well known chemical compounds. As indicated above, some of the reactants of formula (II) are novel, but they can nevertheless be readily prepared
20 by methods well known in the art. For example, compounds of formula (II) can be prepared by the reaction of chlorosulfonylisocyanate with an alcohol of formula



where Hal is chloro or bromo,

5

to give

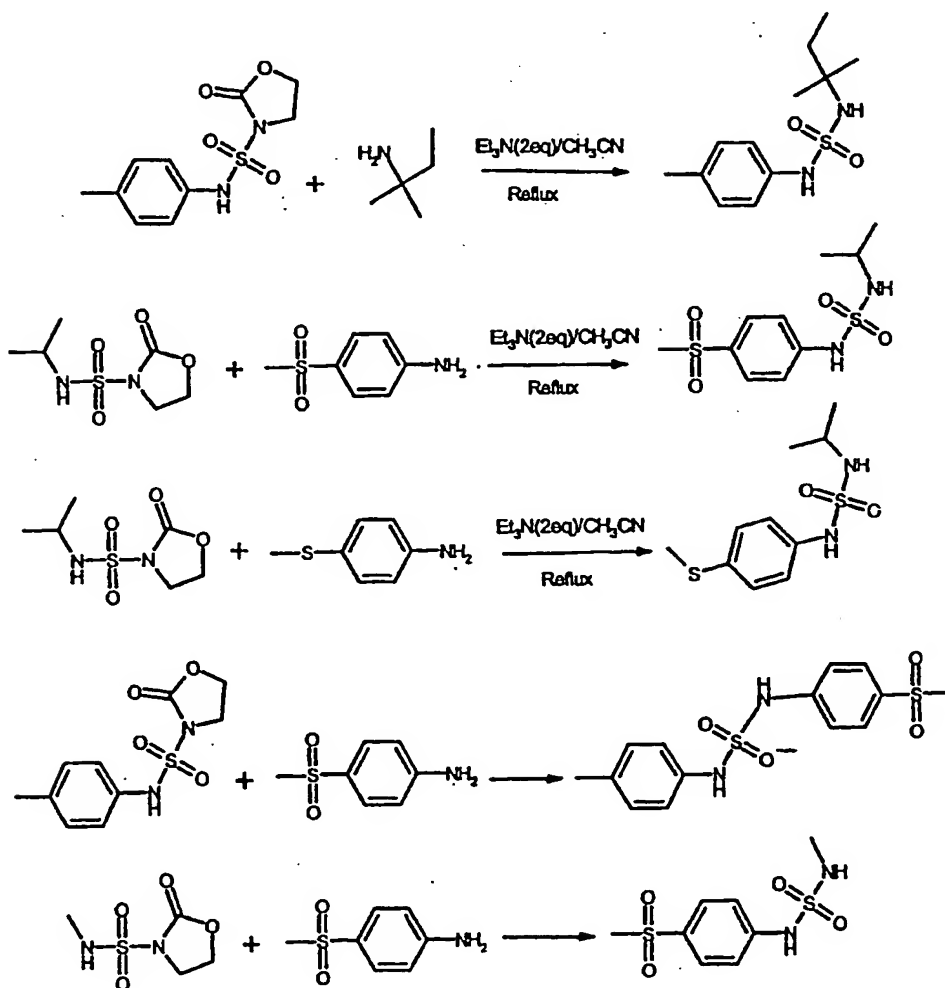


10 which, in turn, when reacted with an amine of formula R^1NH_2 , yields the desired compound of formula (II). The use of an appropriate optically pure alcohol can enable the production of diastereoisomers from which pure chiral

15 sulfamides can be derived.

Examples of reactions according to the invention are as follows:

- 5 The sulfamides of formula (I) can be put to many uses. One such is disclosed in EP-A 0 897921, in which a sulfamide is cyclised to produce a benzothiadiazine dioxide intermediate employed in the preparation of pharmaceutically active compounds.



The following Examples illustrate the invention.

EXAMPLE 1

5

1,1-Dimethylpropylamino-1-sulfonic acid (4-
methylphenyl)-amide

2-Oxo-oxazolidine-3-sulfonic acid (4-methylphenyl)-amide

10

To a 1 L reactor, charged with dichloromethane (176 ml) under an inert atmosphere (N₂) was added chlorosulfonyl isocyanate (CSI) (34.8 ml, 56.6 g, 0.40 mol) and the solution was cooled to 5 °C.

15

A solution of 2-bromoethanol (28.4 ml, 50.0 g, 0.40 mol, 1.0 equiv) in dichloromethane (176 ml) was added to the reaction mixture over 30 minutes under cooling to keep the temperature reaction mixture between 5-7 °C.

20

After stirring for about 30 minutes, a solution of p-toluidine (48.0 g, 0.45 mol, 1.1 equiv) and triethylamine (125 ml, 90.5 g, 0.90 mol, 2.2 equiv) in dichloromethane (358 ml) was added to the reaction

- 10 -

mixture over 30 minutes under cooling to keep the temperature reaction mixture around 5-7 °C.

After a stirring period of about 30 minutes 0.2N HCl
5 (0.4 L) was added. Additional concentrated HCl (37% w/w) was added until the pH of the water layer was ± 2 . After decantation and separation of the aqueous layer, the organic layer was washed with 0.05 N HCl (0.4 L) and water (0.4 L).

10

To the washed and separated organic layer, water (0.4 L) was added followed by the removal of dichloromethane under vacuum. The resulting suspension was stirred for an additional 30 minutes.

15

The reaction mixture was filtered and the filter cake washed with water (0.2 L) and dried at 50 °C under reduced pressure to yield 90.82 g (0.355 mol) of crude 2-oxo-oxazolidine-3-sulfonic acid (4-methylphenyl)-

20 amide.

Crude 2-oxo-oxazolidine-3-sulfonic acid
(4-methylphenyl)-amide (50g) was suspended in dichloromethane (50 ml) and stirred for one hour at room

temperature. The suspension was filtered, washed with dichloromethane (40 ml) and dried under vacuum at 50 °C to yield pure 2-oxo-oxazolidine-3-sulfonic acid (4-methylphenyl)-amide (34.3 g). mp 159-160 °C.

5

1,1-Dimethylpropylamino-1-sulfonic acid (4-methylphenyl)-amide

Triethylamine (3.50 ml, 2.55 g, 25.2 mmol, 2.5 equiv)
10 and tert-amylamine (1.50 ml, 1.12 g, 12.8 mmol, 1.3 equiv) were added to a solution of 2-oxo-oxazolidine-3-sulfonic acid (4-methylphenyl)-amide (2.56 g, 10 mmol, 1.0 equiv) in acetonitrile (12.5 ml). This mixture was heated at reflux for 8 h.

15

After cooling, water (40 ml) was added and the acetonitrile was removed by distillation under vacuum.

Dichloromethane (25 ml) was added to the resulting water
20 emulsion and acidified with 1 ml HCl (37% w/w). After decantation and separation the organic layer was washed with 25 ml 0.05 N HCl and water (25 ml).

The organic layer was concentrated at room temperature under vacuum yielding the crude 1,1-Dimethylpropylamino-1-sulfonic acid (4-methylphenyl)-amide (1.802 g, 7.9 mmol) as a viscous yellow oil which slowly
5 crystallised.

Crude 1,1-Dimethylpropylamino-1-sulfonic acid (4-methylphenyl)-amide (1.40 g, 6.13 mmol) was suspended in hexane (25 ml) and stirred at room temperature during
10 4 h.

The suspension was filtered, and the solid washed with hexane (10 ml). After drying the solid under vacuum at 50 °C, pure 1,1-Dimethylpropylamino-1-sulfonic acid (4-methylphenyl)-amide (609 mg, 2.67 mmol) was obtained. mp
15 92.5-93 °C.

EXAMPLE 2

20 4-Methylphenylamino-1-sulfonic acid
(4-methanesulfonylphenyl)-amide

Triethylamine (7.0 ml, 5.10 g, 50 mmol, 2.5 equiv) and 4-methanesulfonyl-phenylamine (4.28 g, 25 mmol, 1.25

equiv) were added to a solution of 2-oxo-oxazolidine-3-sulfonic acid (4-methylphenyl)-amide (5.12 g, 20 mmol) in acetonitrile (25 ml). This reaction mixture was heated at reflux for 8 hours.

5

After cooling, water (50 ml) was added and the acetonitrile was removed by distillation under vacuum.

To the obtained water emulsion were added
10 dichloromethane (40 ml) and HCl (0.6 ml, 37% w/w).
After decantation and separation of the aqueous layer, 0.05 N HCl (25 ml) was added to the organic layer. At this stage crystallisation occurred. Dichloromethane was removed by distillation under vacuum at room
15 temperature.

The resulting suspension was filtered and the solid washed with water (40ml) and dichloromethane (1 ml). After drying under vacuum at 50 °C, 4-methylphenylamino-
20 1-sulfonic acid (4-methanesulfonylphenyl)-amide (4.64 g, 13.6 mmol) was obtained, mp 165.5-167 °C.

EXAMPLE 3

1-Methylethylamino-1-sulfonic acid
(4-methanesulfonylphenyl)-amide

2-Oxo-oxazolidine-3-sulfonic acid isopropyl-amide

5

To a 250 L glass lined reactor initially charged with dichloromethane (42 L) was added chlorosulfonyl isocyanate (4.5 kg, 31.8 mol) at room temperature and under a nitrogen atmosphere. The reaction mixture was
10 cooled to about 1 °C. and a solution of 2-bromoethanol (4.00 kg, 1 equiv) in dichloromethane (14 L) was slowly added over 51 minutes in order to keep the reaction temperature between 0 and 10 °C. Stirring of the reaction mixture was continued at the same temperature
15 for a minimum of 30 minutes. Progress of the reaction was monitored by ¹H-NMR. A mixture of isopropylamine (2.1 kg, 1.1 equiv) and triethylamine (7.1 kg) in dichloromethane (28 L) was then added at such an addition rate that the reaction temperature was
20 maintained between 0 and 10 °C. The solution was heated up to room temperature. Aqueous hydrochloric acid (~0.2 N, 28.5 kg) was then added and the pH of the reaction mixture was adjusted to about 2 by addition of concentrated hydrochloric acid (450 ml in 2 portions).

The reaction mixture was decanted and the separated organic layer washed with aqueous hydrochloric acid (28.1 kg, ~0.05 N). The decanted and separated organic layer was washed with water (28 kg). To the decanted and separated organic layer, water (28 kg) was then added and the reactor was placed under vacuum to distill the maximum of dichloromethane while controlling the temperature below 25 °C. (84.4 kg of distillate). The resulting suspension was stirred for a minimum of 2 hours at room temperature, filtrated, rinsed twice with water (2 x 7 L) and dried under vacuum at about 50 °C during 16 hours to afford the 2-oxo-oxazolidine-3-sulfonic acid isopropyl-amide, mp 107.5-108.5 °C.

15

1-Methylethylamino-1-sulfonic acid
(4-methanesulfonylphenyl)-amide

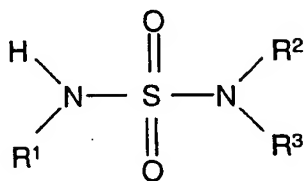
20 A 100 L glass lined reactor was charged with acetonitrile (17.8 kg) and 4-methylsulfonylaniline hydrochloride (3.36 kg, 16.2 mol) under stirring at room temperature. Triethylamine (4.5 kg) and 2-oxo-oxazolidine-3-sulfonic acid isopropyl-amide (3.70 kg,

1.1 equiv) were then added at the same temperature. The reaction mixture was heated to reflux and stirred at the same temperature for a minimum of 6 hours. The solution was then slowly cooled to room temperature and kept
5 agitated over night. Water was slowly added over 40 minutes and the reactor was placed under vacuum to distil as much as possible of acetonitrile (27.8 kg of distillate) while maintaining the reaction temperature below 40 °C. The suspension was cooled to room
10 temperature and stirred for a minimum of 2 hours before filtering the product. The cake was rinsed with water (16.2 kg) and dried under vacuum at about 50 °C. for a minimum of 16 hours to yield the 1-methylethylamino-1-sulfonic acid (4-methanesulfonylphenyl)-amide, mp
15 164-165 °C.

CLAIMS

1. A process for the production of an aryl sulfamide having the formula

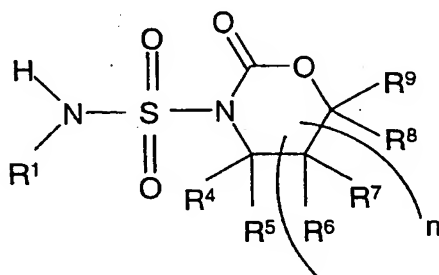
5



in which R¹, R² and R³ are each hydrogen, alkyl, cycloalkyl or aryl, provided that at least one of R¹, R² and R³ is aryl,

10

which comprises reacting a compound of the formula



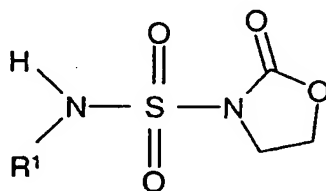
15

where R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are each hydrogen, alkyl or aryl, and n is 0 or 1, with an amine of

the formula R^2R^3NH (III), in the presence of a strong base.

2. A process according to Claim 1 for the production
5 of a compound in which R^1 is alkyl or phenyl optionally substituted with an electron-donating substituent, and R^2 and R^3 are each hydrogen, alkyl or optionally substituted phenyl, provided that R^1 is phenyl optionally substituted with an electron-
10 donating substituent and/or R^2 is optionally substituted phenyl,

which comprises reacting a compound of the formula



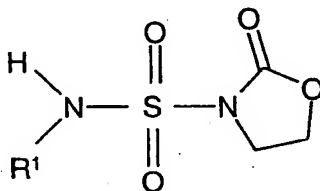
15

with an amine of the formula R^2R^3NH , in the presence of a strong base.

- 20 3. A process according to Claim 2 for the production of a compound in which R^1 is C_{1-6} alkyl or phenyl

optionally substituted with an electron-donating
substituent, R^2 is C_{1-6} alkyl or optionally
substituted phenyl, and R^3 is hydrogen, provided
that R^1 is phenyl optionally substituted with an
electron-donating substituent and/or R^2 is
optionally substituted phenyl.

4. A compound of the formula



where R^1 is phenyl optionally substituted with an
electron-donating substituent are novel, with the
exception of compounds in which R^1 is 3-methylbutyl
or phenyl.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/28877

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C303/34 C07D263/26 C07C307/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	G. DEWYNTER ET AL: TETRAHEDRON, vol. 52, no. 45, 1996, pages 14217-14224, XP004105028 page 14220, line 1 - page 14221, line 17; page 14221, experimental, typical procedures 2.	1,2
A	S.D. MCDERMOTT ET AL: SYNTHESIS, no. 3, 1983, pages 192-195, XP000978880 the whole document	1
A	B. AGOH ET AL: BULL. SOC. CHIM. FR., no. 5, 1987, pages 867-872, XP000978879 page 869, tableau 2, réf. 18	4
	--- -/-- ---	

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

23 January 2001

Date of mailing of the international search report

06/03/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl
Fax (+31-70) 340-3016

Authorized officer

Van Amsterdam, L

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/28877

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>M. ABDAOUI ET AL: TETRAHEDRON LETT., vol. 37, no. 32, 1996, pages 5695-5698, XP004030514 page 5697, table compound 1b -----</p>	4